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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/554,921	10/31/2005	Hiroshi Miura	280271US0X PCT	2311

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EXAMINER	
PALENIK, JEFFREY T	

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
09/17/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/554,921	MIURA ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-35* is/are pending in the application.

4a) Of the above claim(s) *25-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

STATUS OF THE APPLICATION

Applicants' amendments and remarks, filed 6 July 2009 regarding Application N° 10/544,921, are acknowledged and entered on the record. The Examiner acknowledges the following:

Claims 21-35 are pending, where claims 25-35 remain withdrawn from consideration.

Of those claims under consideration, it appears that claim 21 has been amended to clarify the relationship between the pore size and total pore volume. The originally submitted claim 21 has been reviewed and is considered to sufficiently support the amendment (see also Specification at pg. 3).

No new claims have been added and no claims have been cancelled.

The Examiner acknowledges that no new matter has been added to the claims.

Thus, claims 21-24 continue to represent all claims currently under consideration.

INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statements (IDS) have been filed for consideration.

WITHDRAWN OBJECTIONS/REJECTIONS

Rejection under 35 USC 102

Applicants' arguments regarding the rejection of claim 21, under 35 USC 102(b) as being anticipated by Verhoff et al. (US Pre-Grant Publication N° 2002/0047058), have been fully considered and are persuasive.

Applicants have presented their arguments in the form of a Declaration, submitted under 37 CFR §1.132, the crux of which compares the x-ray diffraction limitations recited in claim 21 to those of the preferred silica particles exemplified by Verhoff, namely the silica particles designated "Nyacol 9950".

The procedure employed by Applicants used powder x-ray diffraction as a means to differentiate the two types of particles. The analysis of Applicants' preferred silica material ("FSM-C16") results in a pattern which has two peaks: one having a scattering angle (2Θ) of about 2.3°, whereas the second peak has a scattering angle value of 4°. Using Bragg's equation ($n\lambda = 2d \bullet \sin \Theta$), and using a frequency (λ) value of 0.154 nm for the Cu-Kα radiation, a d-value can be determined for each peak. In the case of both peaks the d-value is greater than 1 nm.

Regarding the Nyacol 9950 diffraction pattern, when Applicants employed the same analysis method, the pattern which resulted gave no peaks. Since there were no discernable peaks, it follows that the Nyacol silica results in a d-value of less than 1 nm.

Thus, in light of the evidence provided against the preferred teachings of Verhoff, it has been shown that Nyacol 9950 does not meet the limitations of the instant base claim with regards to the diffraction limitations. For these reasons, the above rejection is hereby **withdrawn**.

MAINTAINED REJECTIONS

The following rejection is maintained from the previous Office Correspondence dated 12 December 2008 since the art which was previously cited continues to read on the claims as presently amended.

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the

time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verhoff et al. (US Pre-Grant Publication N° 2002/0047058) in view of Takano et al. (USPN 6,753,330).

The instantly amended claims are directed to a composition comprising a extremely poorly water-soluble drug and a porous silica material, as discussed above. Claim 23 further limits the composition by reciting a weight ratio of the drug to the porous material ranging from 0.1:1 to 1:1,000. Claim 12 recites that the drug is the anti-rheumatic composition: 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyradazin-3-one.

The teachings of Verhoff et al. are discussed above (*reproduced here for Applicants' convenience*).

Verhoff et al. teach the preparation of a drug product (e.g. composition) comprising a commixture of small particles of a solid substrate and small particles of a first material, the combination of which is treated (e.g. milled) in the presence of a fluid carrier (claim 1). Said solid substrate is further taught as either a poorly water-soluble or water-insoluble pharmaceutical agent (claims 5 and 6). The small particles of first material are further taught as consisting of silica or colloidal silica (claim 17). Verhoff expressly teaches using drugs which are insoluble in water. The term "insoluble" is interpreted by the Examiner as teaching zero solubility in water, which is less than the recited property limitation of the instantly claimed drug. Furthermore, the "fluid carrier" of claim 1, is further taught in

¶[0149] as comprising a single component or mixture or solution of one or more subcritical or supercritical fluids such as supercritical carbon dioxide.

Verhoff further teaches that the poorly-soluble/water-insoluble active agent may comprise drug classes such as anti-rheumatic agents ¶[0256] and claim 5. Preferred milling media compositions are taught as comprising adjustable concentrations of the solid substrate, fluid carrier and milling media bodies of a first material depending upon the application ¶[0247]. For example, the ratio of the first material (e.g. silica or colloidal silica) to a second material is taught as ranging as broadly from 1:1000 to 1000:1.

Verhoff fails to expressly teach Applicants' claimed ratio range of drug to porous silica material, recited in claim 23, as well as either of Applicants' claimed drug species, recited in claim 24.

Takano et al. teach pharmaceutical solid dispersions comprising the compound: 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyradazin-3-one (Abstract). Said compound is further taught not only as having a generally poor dissolvability in water but also as being of particular use as therapeutic agent for articular rheumatism (col. 1, lines 8-30).

Similar to Verhoff, Takano fails to expressly teach Applicants' claimed drug/porous silica material ratio ranging as instantly claimed.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a composition comprising the combination of an extremely poorly water-soluble drug and a porous silica material as taught by Verhoff and as suggested by the

combination of Verhoff and Takano, modify the ratio of drug to porous silica material, and produce the instantly claimed composition.

One of ordinary skill in the art would have been motivated to do this because Verhoff expressly teaches the instantly claimed silica/drug composition, including preparing said composition by milling in the presence of a fluid carrier such as supercritical carbon dioxide. Though Verhoff does not expressly teach incorporating 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyradazin-3-one as the poorly water-soluble active ingredient complexed in the preparation, the motivation to do so is provided by the fact that Verhoff does teach using active compounds such anti-rheumatic agents as the insoluble solid substrate (see ¶[0256] and claim 5). Coupled with the guidance of the invention to Ohkuchi, the skilled artisan would be well motivated to use the poorly water-soluble species of 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyradazin-3-one in the invention to Verhoff and produce the instant invention.

The combined references do not expressly teach the ratio limitations of poorly-soluble drug to porous material, as instantly claimed by Applicants. Since the values of each parameter with respect to the claimed composition are adjustable, it follows that each is a result-effective parameter that a person having ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. In the instant case, the skilled artisan, would be highly motivated to adjust the aforementioned ratio in view of the teachings presented by Verhoff where it is discussed that the concentrations of the components in the preparation (i.e. the first material, the solid substrate and the milling media) can be optimized based on such

requirements as milling performance and flow characteristics of the substrate to be milled ¶[0247]. Thus, absent some demonstration of unexpected results from the claimed parameters, optimization of any of these parameters would have been obvious at the time of Applicants' invention.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the rejection of claims 21-24 under 35 USC 103(a) as being unpatentable over the combined teachings of Verhoff et al. and Takano et al. have been fully considered but they are not persuasive.

Applicants allege that for the reasons discussed above regarding the porous silica material, the ordinarily skilled artisan would not have had a reasonable expectation of success upon manipulating the silica materials of Verhoff to obtain the porous silica material of claim 21. Applicants rely on this same argument in their traversal of the motivation for combining the two references. Applicants again turn to the Declaration submitted under 37 CFR §1.132 as evidence.

In response, the Examiner respectfully disagrees and submits that the evidence which is provided in the Declaration is not commensurate in scope with the complete teachings of

the combined references.

The Examiner notes that the Declaration is specifically drawn to a comparative analysis between the porous silica material "FSM-C16", and the *preferred* porous silica powder "Nyacol 9950" which is taught by Verhoff (see Examples 1-3). The analysis was conducted using x-ray diffraction-based, as discussed above. Applicants' conclusion to the study (see ¶8) is that compositions using silica material as discussed in the disclosed Examples and such as recited in claim 21, "provides superior dissolution properties relative to known compositions, which are not produced by treating a mixture comprising an extremely poorly water-soluble drug and a porous silica material with a supercritical or subcritical carbon dioxide fluid".

The Examiner has reviewed both of the Examples of the instant disclosure as well as both of the Comparative Examples. Example 1 stirs together "Compound A" (e.g. composition of claim 24), FSM-C16, and dry ice in a "portable reactor" for five hours in order to achieve the instantly claimed composition. Example 2 performs the same procedure except that "FSM-C12" is substituted for "FSM-C16". Comparative Example 1 mixes together the "FSM-C16" and Compound A using a mortar and pestle to achieve particles, whereas Comparative Example 2 repeats the procedure of Examples 1 and 2, but without any silica material. The dissolution rates of each of these four products are tested in order to ascertain the improved dissolution property.

Regarding the comparative analysis provided by the Declaration, it can be clearly proven that the preferred silica material of Verhoff is not the same as that which is used in the instantly disclosed Examples. However, Applicants' conclusion that the compositions which

use silica materials such as those recited by claim 21 (e.g. FSM-C16) provide superior dissolution properties relative to known compositions, is unpersuasive. First, Applicants' "superior dissolution properties" are evidenced against two Comparative Examples, one of which does not employ a silica material and the other of which does not use the same particle-forming method. Furthermore, Applicants' Declaration is directed against only the preferred embodiment which is taught by Verhoff. Regarding this alleged teaching away based on the aforementioned comparative analysis, MPEP §2123 (I), states that "[a] reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art, including non-preferred embodiments". Regarding said embodiments, it is further stated that "[d]isclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiment" (MPEP §2123 (II)). As such the Verhoff reference expressly suggests that embodiments of porous silica material other than Nyacol 9950, may be employed by the practiced invention ¶[0108].

Lastly, with respect to the rejection under 35 USC 103 above, please note that the Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether the porous silica material employed by Applicants' exact composition differs and, if so, to what extent, from that which is expressly taught and suggested by the reference. Therefore, with the showing of the reference, the burden of showing a lack of establishing non-obviousness by objective evidence is shifted to the Applicants.

For these reasons, Applicants' arguments are found unpersuasive. Said rejection is therefore **maintained**.

REQUEST FOR INFORMATION

Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application.

The information is required to identify products and services embodying the disclosed subject matter of the exemplified commercial silicas designated "FSM" by the Toyota Central R&D Labs, Inc. (see pg. 9 of the specification) and identify the properties of similar products and services found in the prior art. A search through the instant application reveals that the "FSM" compounds appear to be a particular species of porous silica material. However, no specific formula or information is disclosed regarding these materials.

In response to this requirement, please provide the title, citation and copy of each publication that any of the applicants relied upon to draft the claimed subject matter. For each publication, please provide a concise explanation of the reliance placed on that publication in distinguishing the claimed subject matter from the prior art.

In response to this requirement, please provide the names of any products or services that have incorporated the claimed subject matter.

The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained may be accepted as a complete reply to the requirement for that item.

This requirement is subject to the provisions of 37 CFR 1.134, 1.135 and 1.136 and has a **shortened statutory period of 2 months**. EXTENSIONS OF THIS TIME PERIOD MAY BE GRANTED UNDER 37 CFR 1.136(a).

All claims under consideration remain rejected; no claims are allowed.

CONCLUSION

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615